WHAT IS CLAIMED IS:

1. An isolated, purified polynucleotide that encodes a mutant Endoplasmic reticulum-associated amyloid β-peptide-binding protein (ERAB) or L-3-hydroxyacryl-CoA dehydrogenase Type II (HADH2) peptide, wherein said peptide is engineered to avoid cysteine oxidation.

2. The polynucleotide of claim 1, wherein said polynucleotide encodes an ERAB or HADH2 peptide which has an amino acid other than cysteine at one or all of positions 5, 58, and/or 214 of SEQ ID NO: 8.

3. An isolated mutant ERAB or HADH2 peptide which is engineered to avoid cysteine oxidation.

4. The peptide of claim 3 which has an amino acid other than cysteine at one or all of positions 5, 58, and/or 214 of SEQ ID NO: 8.

5. A crystal structure of a mutant ERAB or HADH2 peptide wherein said peptide is engineered to avoid cysteine oxidation.

6. The crystal structure of claim 5, wherein said peptide has an amino acid other than cysteine at one or all of positions 5, 58, and/or 214 of SEQ ID NO: 8.

7. An isolated polynucleotide that encodes a mutant ERAB or HADH2 peptide, wherein said polynucleotide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 19, and SEQ ID NO: 22, and functional variants thereof.

8. An isolated polynucleotide that encodes a mutant ERAB or HADH2 peptide, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

9. A crystal structure of a mutant ERAB or HADH2 peptide, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and fragments or variants thereof.

10. The crystal structure of claim 9, wherein said mutant peptide has an amino acid sequence of SEQ ID NO: 2, or fragments or variants thereof.

11. The crystal structure of claim 9, wherein said mutant peptide has an amino acid sequence of SEQ ID NO: 4, or fragments or variants thereof.

12. The crystal structure of claim 9, wherein said mutant peptide has an amino acid sequence of SEQ ID NO: 6, or fragments or variants thereof.

13. The crystal structure of claim 9, wherein said mutant peptide has an amino acid sequence of SEQ ID NO: 20, or fragments or variants thereof.

14. The crystal structure of claim 9, wherein said mutant peptide has an amino acid sequence of SEQ ID NO: 23, or fragments or variants thereof.

15. The crystal structure of claim 5, 6 or 9, wherein said crystal diffracts x-rays at a resolution value of ≤ 3 Å.

16. The crystal structure of claim 5, 6 or 9, wherein said crystal diffracts x-rays at a resolution value of ≤ 2 Å.

17. The crystal structure of claim 5, 6, or 9, wherein said crystal peptide mutant is tetrameric.

18. A crystal structure of a mutant ERAB or HADH2 peptide:ligand:NAD^+ complex wherein said peptide is engineered to avoid cysteine oxidation.

19. The crystal structure of claim 18, wherein said peptide has an amino acid other than cysteine at one or all of positions 5, 58, and/or 214 of SEQ ID NO: 8.

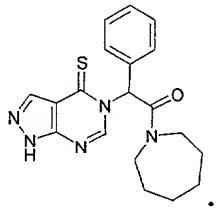
20. A crystal structure of a mutant ERAB or HADH2 peptide:ligand:NAD^+ complex, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

21. The crystal structure of claim 18, 19 or 20, wherein the crystal diffracts X-rays for the determination of the atomic coordinates of the complex to a resolution of greater than 3.0Å.

22. The crystal structure of claim 20 having the crystal coordinates shown in Table II.

23. The crystal structure of claim 18, 19 or 20, wherein said ligand is an ERAB or HADH2 inhibitor.

24. The crystal structure of claim 18, 19 or 20, wherein said ERAB or HADH2 inhibitor is a compound of the formula:



25. An isolated, purified peptide comprising a mutant ERAB or HADH2 peptide, wherein said mutant peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

26. The peptide of claim 25 having an amino acid sequence comprising amino acids 90 to 261 of SEQ ID NO: 2 or functional variants thereof.

27. An isolated, purified ERAB or HADH2 peptide comprising a fold, wherein said fold comprises: a core β-sheet of seven strands sandwiched between two sets of three α-helices; and first and second insert domains, relative to other members of the short-chain dehydrogenase/reductase (SDR) family, the first insert domain forming a β hairpin that extends the surface of said ERAB or HADH2 peptide on one side of a substrate-binding cleft, and the second insert domain extending a loop between an α-helix and a β-sheet, wherein said α-helix comprises amino acid residues having a sequence of amino acid 123-136 of SEQ ID NO: 2, and said β-sheet comprises amino acid residues having a sequence of amino acid 148-153 of SEQ ID NO: 2.

28. An isolated, purified mutant ERAB or HADH2 peptide comprising a fold, wherein said fold comprises: a core β-sheet of seven strands sandwiched between two sets of three α-helices; and first and second insert domains, relative to other members of the short-chain dehydrogenase/reductase (SDR) family, the first insert domain forming a β hairpin that extends the surface of said ERAB or HADH2 peptide on one side of a substrate-binding cleft, and the second insert domain extending a loop between an α-helix and a β-sheet, wherein said peptide is engineered to avoid cysteine oxidation.

29. The peptide of claim 28, wherein said peptide has an amino acid other than cysteine at one or all of positions 5, 58, and/or 214 of SEQ ID NO: 8.

30. The peptide according to claim 28, wherein said α-helix comprises amino acid residues having a sequence of amino acid 123-136 of SEQ ID NO: 2 and said β-sheet comprises amino acid residues having a sequence of amino acid 148-153 of SEQ ID NO: 2, and further comprises a substrate-binding site involving residues selected from the group consisting of
(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;
(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;
(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;
(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and
(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

31 An isolated, purified mutant ERAB or HADH2 peptide comprising a fold, wherein said fold comprises: a core β-sheet of seven strands sandwiched between two sets of three α-helices; and first and second insert domains, relative to other members of the short-chain dehydrogenase/reductase (SDR) family, the first insert domain forming a β hairpin that extends the surface of said ERAB or HADH2 peptide on one side of a substrate-binding cleft, and the second insert domain extending a loop between an α-helix comprising residues 123-136 and a β-sheet comprising residues 148-153 of SEQ ID NO: 2.

32. The peptide according to claim 27, 28 or 31, further comprising a substrate-binding site involving residues selected from the group consisting of
(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;
(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;
(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;
(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and
(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

33. The peptide according to claim 31, wherein said first insert domain is at residues 102-107 of SEQ ID NO: 2.

34. The peptide according to claim 31, wherein said second insert domain is at residues 141-146 of SEQ ID NO: 2.

35. The peptide according to claim 31, wherein said ERAB or HADH2 is in the form of monomer.

36. The peptide according to claim 35, wherein said ERAB or HADH2 monomer forms a tetramer when crystallized.

37. The peptide according to claim 36, further comprising an ERAB or HADH2 cofactor-binding site.

38. The peptide according to claim 37, wherein said ERAB or HADH2 cofactor is NAD^+.

39. An expression vector for producing a mutant ERAB or HADH2 peptide in a host cell, which vector comprises: a polynucleotide that encodes a mutant ERAB or HADH2 peptide, wherein said polynucleotide is the polynucleotide of claim 1, 2, or 7, or functional variants thereof; transcriptional regulatory sequences functional in said host cell operably linked to said polynucleotide; and a selectable marker.

40. The vector of claim 39, wherein said polynucleotide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 19, and SEQ ID NO: 22, and functional variants thereof.

41. A host cell stably transfected and transformed with the polynucleotide that encodes a mutant ERAB or HADH2 peptide, wherein said polynucleotide is the polynucleotide of claim 1, 2, or 7, or functional variants thereof.

42. The host cell of claim 41, wherein said polynucleotide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 19, and SEQ ID NO: 22, and functional variants thereof.

43. A method for identifying a candidate compound for its ability to interact with the human ERAB or HADH2 peptide comprising:
    (a) expressing an isolated polynucleotide sequence which encodes a mutant ERAB or HADH2 peptide in a host cell capable of producing said peptide, wherein said polynucleotide is the polynucleotide of claim 1, 2, or 7, or functional variants thereof;
    (b) exposing said mutant ERAB or HADH2 peptide to said candidate compound; and
    (c) evaluating the interaction of said mutant ERAB or HADH2 peptide with said candidate compound.

44. The method of claim 43, wherein said polynucleotide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 19 and SEQ ID NO: 22, and functional variants thereof.

45. The method of claim 43, wherein said evaluation step comprises conducting said x-ray crystallography on said ERAB or HADH2 peptide.

46. The method of claim 45, wherein the results of said x-ray crystallography step are used to determine the three-dimensional molecular structure of the configuration of the ERAB or HADH2 peptide and the binding pockets thereof.

47. A process of drug design for compounds which interact with an ERAB or HADH2 peptide comprising:
    (a) crystallizing a mutant ERAB or HADH2 peptide, said peptide being a peptide of claim 3, 4, or 25, or functional variants thereof;
    (b) resolving the x-ray crystallography of said peptide;
    (c) applying the data, or a portion thereof, generated from resolving the x-ray crystallography of said peptide to a computer algorithm which generates a model of a three-dimensional structure, said model suitable for use in designing molecules that will interact with said peptide; and
    (d) applying an interative process whereby various molecular structures are applied to said computer-generated model to identify the compounds which interact with said peptide.

48. The method of claim 47, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

49. The method of claim 47, wherein said process is utilized to identify inhibitors of an ERAB or HADH2 enzyme, said inhibitors serving as lead compounds for the design of potentially therapeutic compounds for the treatment of diseases or disorders associated with the ERAB or HADH2 action.

50. A method of assessing compounds which are agonists or antagonists of the activity of the human ERAB or HADH2 enzyme comprising:
    (a) crystallizing a mutant ERAB or HADH2 peptide, said peptide being a peptide of claim 3, 4, or 25, or functional variants thereof;
    (b) obtaining crystallography coordinates for said crystallized peptide;
    (c) applying said crystallography coordinates or a portion thereof for said peptide to a computer algorithm such that said algorithm generates a model of a three-dimensional structure, said model suitable for use in designing molecules that will act as agonists or antagonists to said peptide; and
    (d) applying an iterative process whereby various molecular structures are applied to said computer-generated model to identify potential agonists or antagonists to said peptide.

51. The method of claim 50, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

52. A method of identifying a compound that associates with an ERAB or HADH2 peptide, the method comprising the step of using the crystal coordinates of Table II or a portion thereof to computationally analyze a molecular structure to evaluate a chemical entity for associating with the substrate-binding site of ERAB or HADH2 and identifying those chemical entities that associate with said substrate-binding site, wherein said step of computationally analyzing the molecular sturucture comprises:
    (a) storing instructions for processing machine readable data wherein said data comprises crystal coordinates of a mutant ERAB or HADH2 peptide molecule or complex of said peptide, said mutant ERAB or HADH2 peptide being the peptide of claim 3, 4, or 25, or functional variants thereof; and
    (c) processing said data of crystal coordinates into a three-dimensional structure of said peptide molecule or complex.

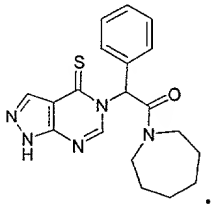
53. The method of claim 52 further comprising the step of displaying said crystal coordinates of the three-dimensional structure.

54. The method of claim 52, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereof.

55. The method of claim 52, wherein said complex is an ERAB or HADH2 peptide:ligand:NAD^+ complex.

56. The method of claim 55, wherein said ligand is an ERAB or HADH2 inhibitor.

57. The method of claim 56, wherein said ligand is a compound of the formula:



58. A method of using a computer processor for analyzing a molecular structure comprising:
    (a) storing instructions for processing machine readable data wherein said data comprises crystal coordinates of a mutant ERAB or HADH2 peptide molecule or complex of said peptide, said mutant ERAB or HADH2 peptide being the peptide of claim 3, 4, or 25, or functional variants thereof; and
    (b) processing said data of crystal coordinates into a three-dimensional structure of said peptide molecule or complex.

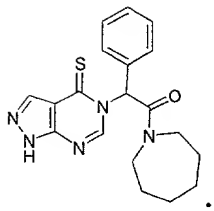
59. The method of claim 58 further comprising the step of displaying said crystal coordinates of the three-dimensional structure.

60. The method of claim 58, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 23, and functional variants thereo

61. The method of claim 58, wherein said complex is an ERAB or HADH2 peptide:ligand:NAD^+ complex.

62. The method of claim 61, wherein said ligand is an ERAB or HADH2 inhibitor.

63. The method of claim 62, wherein said ligand is a compound of the formula:



64. The method of claim 58, wherein said machine readable data storage medium is CD-ROM.

65. The method of claim 58, wherein said machine readable data storage medium is a magneto-optic disk.

66. A computer based method for processing X-ray coordinate data into a three-dimensional graphical display of a mutant ERAB or HAHD2 peptide molecule or molecular complex which comprises a substrate binding domain, wherein said mutant ERAB or HADH2 peptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 20 and SEQ ID NO: 23, and functional variants thereof.

67. The method of claim 66, wherein said complex is an ERAB or HADH2 peptide:ligand:NAD^+ complex.

68. The method of claim 67, wherein said ligand is an ERAB or HADH2 inhibitor.

69. The method of claim 66, wherein said X-ray coordinate data is stored in a machine readable storage medium.

70. The method of claim 66, wherein said three-dimensional graphical display is displayed on a computer monitor.

71. A crystallized ERAB or HADH2 peptide or an ERAB or HADH2 peptide:cofactor:ligand complex containing a substrate-binding site comprised of amino acid residues selected from the group consisting of

(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;

(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;

(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;

(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 8;

(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and

(f) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

72. The crystallized peptide or complex of claim 71, wherein said cofactor is NAD^+.

73. A method of assessing compounds which are agonists or antagonists of the activity of the human ERAB or HADH2 pepetide comprising:

(a) crystallizing an ERAB or HADH2 peptide or ERAB or HADH2 peptide:NAD^+:ligand complex;

(b) obtaining crystallography coordinates for said crystallized peptide or complex;

(c) applying said crystallography coordinates or a portion thereof for said peptide to a computer algorithm such that said algorithm generates a model of a substrate-binding site, said model suitable for use in designing molecules that will act as agonists or antagonists to said peptide; and

(d) applying an iterative process whereby various molecular structures are applied to said computer-generated model to identify potential agonists or antagonists to said peptide.

74. The method of claim 73, wherein said substrate-binding site comprises amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II.

75. A method of assessing compounds which are agonists or antagonists of the activity of the human ERAB or HADH2 peptide comprising:

(a) employing computational means to perform a fitting operation between the compounds and a substrate-binding site defined by crystallographic coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II; and

(b) applying an iterative process whereby various molecular structures are applied to said fitting operation to identify potential agonists or antagonists to said peptide.

76. The method of claim 75, wherein said substrate-binding site has amino acid residues selected from the group consisting of

(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;

(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;

(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;

(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 8;

(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and

(f) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

77. A method of identifying a compound that associates with ERAB or HADH2, the method comprising the step of using the crystal coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II to computationally analyze a molecular structure to evaluate a chemical entity for associating with the substrate-binding site of ERAB or HADH2 and identifying those chemical entities that associate with said substrate-binding site, wherein said step of computationally analyzing the molecular structure comprises:
    (a) storing instructions for processing machine readable data wherein said data comprises crystal coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II; and
    (b) processing said data of crystal coordinates into a three-dimensional structure of said peptide molecule or complex.

78. The method of claim 77 further comprising the step of displaying said crystal coordinates of the three-dimensional structure.

79. A method of using a computer processor for analyzing a substrate-binding site of an ERAB or HADH2 peptide or ERAB or HADH2 peptide:NAD^+:ligand complex comprising:
    (a) storing instructions for processing machine readable data wherein said data comprises X-ray crystallographic coordinates having crystal coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II; and
    (b) processing said data of crystal coordinates into a three-dimensional structure of said peptide molecule or complex to analyze the substrate-binding site of said peptide.

80. The method of claim 79 further comprising the step of displaying said crystal coordinates of the three-dimensional structure.

81. The method of claim 79, wherein said ligand is an ERAB or HADH2 inhibitor.

82. The method of claim 79, wherein said machine readable data storage medium is CD-ROM.

83. The method of claim 79, wherein said machine readable data storage medium is a magneto-optic disk.

84. A computer based method for processing X-ray coordinate data into a three-dimensional graphical display of a substrate-binding site of an ERAB or HADH2 peptide molecule or

ERAB or HADH2 peptide:NAD^+:ligand complex using the crystal coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II.

85. The method of claim 84, wherein said ligand is an ERAB or HADH2 inhibitor.

86. The method of claim 84, wherein said X-ray coordinate data is stored in a machine readable storage medium.

87. The method of claim 84, wherein said three-dimensional graphical display is displayed on a computer monitor.

88. A process of drug design for compounds which associate with a substrate-binding site of an ERAB or HADH2 peptide comprising:
(a) employing computational means to perform a fitting operation between the compounds and a substrate-binding site defined by crystallographic coordinates of amino acid residues 95 to 99, 155 to 168, 205 to 213, 215-217, and 257 to 261 of SEQ ID NO: 2 according to Table II; and
(b) applying an iterative process whereby various molecular structures are applied to said fitting operation to identify the compounds which associate with the substrate-binding site.

89. The method of claim 88, wherein said substrate-binding site has amino acid residues selected from the group consisting of
(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;
(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;
(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;
(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 8;
(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and
(f) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

90. The method of claim 73 or 79, wherein said substrate-binding site has amino acid residues selected from the group consisting of
(a) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2;
(b) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 4;
(c) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 6;

(d) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 8;

(e) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 20; and

(f) residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 23.

91. A method of identifying a compound that associates with an ERAB or HADH2 peptide, the method comprising using the crystal coordinates from Table II, or portions thereof, to computationally evaluate a chemical entity for associating with the substrate-binding site of ERAB or HADH2.

92. A computer readable medium having stored thereon a model of a crystal structure comprising an ERAB or HADH2 peptide wherein said peptide has a substrate-binding site containing amino acid residues 95 to 99, 155 to 168, 205 to 217, and 257 to 261 of SEQ ID NO: 2.